14. The cytokine inducers according to any one of claims 11 to 13, wherein the protein M161Ag is acylated with fatty acid in the N-terminal thereof.

**REMARKS**

Claims 1 and 3-5 have been cancelled, and claims 11-14 have been added. No new matter has been added by virtue of the amendments made to the claims, support therefore being found throughout the specification and in the original claims of the application.

As an initial matter, Applicants appreciate the reconsideration and withdrawal of the finality of the previous Office Action.

Referring to the Office Action, an objection to the Specification is noted. In particular, the Office Action indicates that the Supplemental Information Disclosure Statement filed on May 15, 2002 (Paper No. 14) was incomplete in that it did not list the disclosure date or name of the relevant publication.

Applicants submit herewith a substitute Supplemental Information Disclosure Statement/PTO 1449 Form which reflects all required information. As the objection is understood, the within submission will be treated as a mere correction to the earlier filing, thus no fee should be due. If that assumption is incorrect, kindly charge the undersigned firm's Deposit Account 04-1105.

The following rejections are discussed in combination.

Claims 1 and 3-5 stand rejected under 35 USC §101. As the rejection is understood, it is alleged that the noted claims are directed to non-statutory subject matter.

Claims 1 and 3-5 stand rejected under 35 USC §112, second paragraph, on the grounds of

indefiniteness.

Claims 3 and 4 are further objected to under 37 CFR §1.75(c), as allegedly lacking proper dependent form.

It is believed that each of the afore-mentioned rejections is obviated by the within amendments. In particular, Applicants have cancelled claims 1 and 3-5, and rewritten the subject matter thereof in new claims 11-14. New claim 11 recites "An isolated or purified cytokine inducer comprising a protein M161Ag"..., which is believed to obviate the §101 rejection. Additionally, the phrase "gene recombination products" is not recited in the new claims, thus obviating the §112, 2nd paragraph rejection. Further, the new claims are presented in proper dependent form, thus obviating the objection under 37 CFR §1.75(c).

Reconsideration and withdrawal of each of these rejections are thus requested.

Claims 1 and 3-5 stand rejected under 35 USC §112, first paragraph, on the grounds of enablement and written description.

The Office Action acknowledges that the specification is enabling for cytokine inducers comprising a lipoprotein Mycoplasma fermentans 161Ag having a polynucleotide sequence of SEQ ID NO. 1, wherein the cytokines induced are selected from: IL-6, IL-10, IL-12, TNF-α, IFN-γ, and IL-1β. However, the position is taken that the specification is allegedly non-enabling for induction of any other cytokine inducers from *M. fermentans* or any other gene recombination products. Further, the position is taken that the specification is allegedly non-enabling for a method of use of cytokine inducers as immunomodulators.

While Applicants believe the former claims 1 and 3-5 fully meet the enablement and written description requirements of 35 USC §112, first paragraph, it also is submitted that the rejection is obviated by the amendments herein. In particular, in order to expedite prosecution of

the application, the subject matter of former claims 1 and 3-5 has been rewritten in new claims 11-14. The newly presented claims do not recite the phrase "gene recombination products". Additionally, the newly presented claims further define and clarify the features of the present invention.

In view thereof, reconsideration and withdrawal of the rejection under §112, first paragraph, are requested.

The prior art rejections are summarized as follows.

Claims 1 and 3-5 stand rejected under 35 USC §102(b), in view of Matsumoto et al. (*J. Exp. Med.*, 1995).

Claims 1 and 3-5 stand rejected under 35 USC §102(a), in view of Matsumoto et al. (*Nature Medicine*, 1997).

Claims 1 and 3-5 stand rejected under 35 USC §102(a), in view of JP 9-157295 (June 1997).

Claims 1 and 3-5 stand rejected under 35 USC §102(b), in view of Rawadi et al. (1996).

Each of the rejections is traversed. None of the cited references teach or suggest the cytokine inducers of the present invention.

For instance, the 1995 Matsumoto et al. reference teaches the deposit of human C3 fragments on M161Ag (see Matsumoto at page 121, left column, line 30 - right column, line 8). The Office Action asserts that the 1995 Matsumoto et al. reference also teaches that M161Ag is a potent activator of the human alternative complement pathway on human cells that activates homologous C3, and allows the deposition of C3b on itself (reference is made to Matsumoto's

Abstract, last 4 lines).

Applicants submit that the 1995 Matsumoto et al. reference does not teach or suggest the features of the present invention. Indeed, the cited document does not teach or suggest that the C3 activation and deposition on human cells would induce cytokine production. Further, Matsumoto et al. does not teach or suggest that the M161Ag protein induces cytokine production.

Moreover, it is respectfully submitted that M161Ag is a dual functional protein in which the acylated N-terminal domain of M161Ag activates cytokine production via the Toll-Like Receptor 2 signaling pathway, and the whole region of M161Ag activates the human complement pathway. Still further, the cytokine induction by M161Ag is mediated by Toll-Like Receptor 2 signaling pathway and not by the human complement pathway. Therefore, the cytokine inducing function of M161Ag cannot be anticipated by the complement activating ability of M161Ag.

In support of the above arguments, submitted herewith is a copy of the following document: "Structural and Functional Properties of Complement-Activating Protein M161Ag, a *Mycoplasma fermentans* Gene Product That Induces Cytokine Production by Human Monocytes" (Matsumoto et al., 1998, *J. Biol. Chem.*, Vol. 273, No. 20, pp. 12407-12414). That document, cited in an earlier filed Information Disclosure Statement, was published after the present application's priority filing date. As discussed therein, M161Ag is highly homologous in the N-terminal region to P48. P48 is a monocyte differentiation/activation factor originating from *M. fermentans*. P48, as well as M161Ag, induces the production of IL-1β, TNF-α, and IL-6 in human monocytes and monocytic cell lines. It is stated in that Matsumoto et al. reference that the IL-1β, TNF-α, and IL-6 inducing activity must be mapped within the N-terminal domain conserved between M161Ag and P48, because the amino acid sequences are largely different throughout the C-terminal region between these two proteins (see page 12412, left column, lines 1-5). Additionally, C-activation ability has not been determined in P48 (page 12412, left column, bottom line - right column line 1). These facts demonstrate that the M161Ag is a dual functional

protein in which the cytokine inducing function is separate from the complement activating function.

Subsequent to the afore-mentioned 1998 Matsumoto et al. publication, the MALP-2 was identified as a ligand for Toll-like receptor 2 (TLR2) by Lien et al. MALP-2 is a 14-amino-acid lipopeptide and quite similar to the N-terminal region of M161Ag. Attention is directed to figure 2 in the second of the two enclosed support documents: "Toll-like Receptor 2 Functions as a Pattern Recognition Receptor for Diverse Bacterial Products" (Lien et al., 1999, *J. Biol. Chem.*, Vol. 274, No. 47, pp. 33419-33425). Toll-like receptors are involved in activation of NF-κB, p38 mitogen-activated protein kinase, and Jun N-terminal kinase, leading to the induction of proinflammatory action including cytokine production. These facts indicate that the cytokine induction by M161Ag is mediated by Toll-like Receptor 2 signaling pathway and not by the human complement pathway.

Referring now to the rejection under 35 U.S.C. §102(a) in view of Matsumoto et al., *Nature Medicine,* 1997, Applicants submit the following arguments. The 1997 Matsumoto et al. reference reports the success of cloning cDNA encoding M161Ag protein from a plasmid cDNA library which originated from a human myeloid cell subline P39(+) (see Matsumoto 1997 at page 1266, left column, lines 24-39). Additionally, Matsumoto et al. speculate that M161Ag protein is bound to cells and activates homologous C3 and allows C3 deposition (see Matsumoto 1997 at page 1268, left column, line 22 – right column, line 1).

However, the 1997 Matsumoto et al. provides no teaching, e.g., data, or even suggestion that the C3 activation and deposition on human cells induce cytokine production. Additionally, the 1997 Matsumoto et al. reference provides no teaching or suggestion that the M161Ag protein induces cytokine production.

Moreover, as discussed above, M161Ag is a dual functional protein in which the acylated N-terminal domain of M161Ag activates cytokine production via Toll-Like Receptor 2 signaling

pathway, and the whole region of M161Ag activates the human complement pathway. The cytokine induction by M161Ag is mediated by Toll-Like Receptor 2 signaling pathway and not by the human complement pathway. Therefore, the cytokine inducing function of M161Ag cannot be anticipated by the complement activating ability of M161Ag.

JP No. 9-157295 (June 1997) is likewise deficient. JP 9-157295 discloses M161Ag cDNA sequence which is obtained from a plasmid cDNA library originating from a human myeloid cell subline P39(+). It is described that M161Ag allows the second complement pathway activation and C3 deposition (see JP 9-157295 at section [0002]).

As with the earlier described cited references, JP 9-157295 does not teach or suggest that the C3 activation and deposition on human cells induce cytokine production. Additionally, JP 9-157295 provides no teaching or suggestion that M161Ag protein induces cytokine production. Moreover, Applicants arguments above with respect to M161Ag being a dual functional protein are repeated.

Rawadi et al. also is deficient. That document discloses that Heat-Inactive Mycoplasma (*HIM*) particles induce inflammatory cytokines such as IL-1, IL-6, and TNF in monocytes. Rawadi teaches that cytokine inducing activity of *M fermentans* is mediated by lipid-associated molecule (see the Rawadi Abstract and Figure 3).

However, Rawadi et al. provides no description indicating what molecule induces cytokine production, except the term "lipid–associated molecules" or "Mycoplasma particles". Accordingly, the cytokine induction activity of M161Ag cannot be anticipated by Rawadi et al.

In addition, M161Ag had been earlier misunderstood as a human gene product, e.g., prior to filing of the present application. Attention is directed to the enclosed document, Matsumoto et al., 1998, *J.Biol.Chem*, at page 12407, right column, line 14-16. Thus, clearly the cytokine inducing ability of M161Ag could not be anticipated by Rawadi et al.

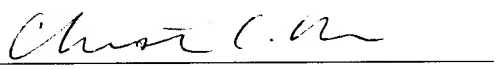
Accordingly, each of the prior art rejections is properly withdrawn. Indeed, in order to anticipate a claim, a single reference must disclose each and every element of the claim. For example, see *In re Marshall*, 198 USPQ 344, 346 (CCPA 1978) ("[r]ejections under 35 U.S.C. §102 are proper only when the claimed subject matter is identically disclosed or described in the prior art.").

In any case, Applicants believe that the amendments submitted herein obviate the rejection. In particular, claims 1 and 3-5 have been cancelled. The subject matter of those claims has been rewritten in new claims 11-14 in order to further define and clarify the features of the present invention.

Reconsideration and withdrawal of the rejections are thus requested.

It is believed the application is in condition for immediate allowance, which action is earnestly solicited.

Respectfully submitted,



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**VERSION MARKED TO SHOW CHANGES**

**IN THE CLAIMS**

Claims 1 and 3-5 were cancelled without prejudice.

New claims 11-14 were added.